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Registry and Biospecimen Repository

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13. ABSTRACT (Maximum 200 Words)
The Inflammatory Breast Cancer Registry (IBCR) enrolled its first patient Sept. 10, 2002 after completing all necessary IRB and HIPAA pre-study requirements. As of Nov. 1, 2003, 120 patients have asked to be enrolled in the IBCR and 110 have completed their interviews. Tissue blocks have been obtained from 51 patients and frozen surgical specimens have been collected form 10. A Biospecimen Advisory Board was established and procedures are now in place to send biospecimens to requesting laboratories on a pilot basis and determine the number of subsequent specimens sent based on the initial results. Five laboratories are currently collaborating with multiple assays being performed by three of them. The lessons learned from the first 50 patients are being presented at the San Antonio Breast Cancer Conference in Dec 2003. The data include the observation that approximately one third of IBC patients are initially diagnosed as having mastits and are treated with up to five months of antibiotics before the diagnosis of cancer is made. Less than 25% of patients have a discrete mass identified on initial mammography. Most patients received standard IBC therapy (chemotherapy followed by mastectomy, additional chemotherapy and radiation) but some were not offered surgery.

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INTRODUCTION

Studying inflammatory breast cancer (IBC), the most aggressive form of breast cancer, may provide an understanding of aggressive breast cancer and the biology of breast cancer in general. Since IBC is relatively rare, we have developed a national registry of patients with IBC which contains standardized clinical, epidemiological and pathological information. Our registry includes both the clinical classification (redness, warmth, and edema) and the pathological classification (invasion of the dermal lymphatics). By standardizing clinical and pathologic information, we have an excellent opportunity to investigate the heterogeneity of IBC. We are characterizing the tumors of the IBC patients by using a panel of biomarkers through the implementation of a biospecimen repository. The specimens we collect include formalin fixed material (stained and unstained) and frozen tissue (normal and tumor). New technological advancements in molecular biology have made it possible to study biomarkers in these tumors. The specimens are needed more than ever to provide opportunities for critical translational research focusing on the pathogenesis of breast malignancies. We currently work with five laboratories. We will also make our specimens available to qualified investigators for new studies to facilitate their research. This registry will serve as a source of useful epidemiological data for investigators who are studying IBC and can be used to generate hypotheses that might be tested in subsequent epidemiological studies.

BODY

The purposes of this project are: 1) to develop a well-documented Registry of patients with IBC, 2) to establish a bank of biospecimens and 3) improve the diagnostic criteria for IBC. The repository will be made available to researchers who are doing research on the etiology and pathogenesis of IBC.

Tasks (objectives of project)

1. To identify patients with IBC who are willing to provide relevant information.

   We have developed close communication with two Web-based IBC support groups that inform patients how to contact the IBC registry. As of Nov. 1, 2003, 120 patients have asked to be enrolled in the IBCR.

2. To develop a questionnaire to obtain epidemiological information on IBC patients. The questionnaire is based on findings from previous studies on IBC and aggressive breast cancer and other reports of relevant factors.

   The questionnaire has been completed and 103 women have been interviewed to date (Appendix 1). The principal investigator also interviews each patient to gather clinical information which helps to classify each patient according to category (see Table 1).

Table 1: Case Categories

Group 1: Classical history and physical findings, pathological confirmation
Group 2: Classical history and physical findings, no pathological confirmation
Group 3: Incomplete clinical findings of IBC, pathological confirmation
Group 4: Incomplete clinical findings of IBC, no pathological confirmation
Group 5: Pathologic findings without clinical features
Group 6: IBC vs. neglected breast cancer
Group 7: Apparent neglected breast cancer

3. To obtain paraffin blocks, and when feasible, freshly frozen tissues to establish a biospecimen repository.

Tissue blocks have been obtained from 51 patients and frozen surgical specimens have been collected from 10. A Biospecimen Advisory Board was established and procedures are now in place to send biospecimens to requesting laboratories on a pilot basis and determine the number of subsequent specimens to be sent based on the initial results. Five laboratories are currently collaborating with multiple assays being performed by three of them.

4. To collect and enter into a database information from the questionnaire, information on recurrence and survival, clinical and pathological information, and information on the presence of biomarkers.

Two password protected access databases have been created to store data from the questionnaire and from the principal investigator's interview.

5. To make biospecimen repository available to researchers.

The Principal Investigator, Dr. Paul Levine, has presented the project and the availability of biospecimens to researchers at the 2002 San Antonio Cancer Conference in San Antonio and will again describe the availability at a presentation in the 2003 San Antonio Breast Cancer. All publications involving the IBC Registry will include this information.

Current findings from analysis of first 50 cases

Of the first 50 patients, 46 contacted us through the Internet and four were referred by GW physicians. Patients were diagnosed and treated in 23 different states and 2 Canadian provinces. Geographic characteristics of patients were widespread involving rural as well as urban areas.

Table 2 : Initial Diagnosis

Initial Diagnosis	Number	Percent
Breast Cancer	30	60%
Mastitis	10	20%
Breast Cancer vs. Mastitis	4	8%
Cyst	3	6%
Ductal Papilloma	1	2%
Nothing to worry about	1	2%
Other	1	2%

Table 3 : Presenting Symptoms

Symptom	Number	Percent
Redness	28	56%
Enlargement	27	54%
Pain	17	34%
Peau d'orange	16	32%
Warmth	16	32%
Inverted nipple	11	22%
Discrete Lump	9	18%
Itching	8	16%
Thick mass	7	14%

Table 4: First Cancer Treatment Received

Type of Treatment	Number of Pts.	Percent
Chemotherapy	43	86%
Lumpectomy	5	10%
Mastectomy	1	2%
Radiation	1	2%

Table 5: Overall Treatment

Type of Treatment	Frequency	Percent
Mastectomy	47	94%
Radiotherapy	44	88%
Chemotherapy	50	100%
BMT-SCT (Bone marrow or stem cell transplant)	6	12%
Other treatment	3	6%

Among other findings of the first 50 cases, eleven patients (22%) were initially treated with antibiotics up to 5 months. Four women died from IBC; two were in categories 4 and 5 and would not have been considered to have IBC by American Joint Committee on Cancer (AJCC) criteria. Mammograms on 70% of patients did not show any discrete mass. Sixty percent were ER positive and 38% were Her2 Neu positive.

Problems in accomplishing tasks
There were no apparent problems in accomplishing the tasks, although we do not have the African-American involvement we would have preferred. Only two African-American woman are in the first 100 patients although IBC is more common in African-American women than Caucasian Women.

Statistical test of significance
No statistical tests of significance have been performed at the current time.

Recommended changes or future work
We believe the current procedures and progress are appropriate and expect a successful outcome. We will continue on the collection and analysis of the following data:
- Molecular characterization of IBC.
- Correlation of presenting signs and symptoms, initial response to treatment, and survival.
- Molecular identification of markers of resistance to chemotherapy.
- Further characterization of risk factors for IBC.

KEY RESEARCH ACCOMPLISHMENTS

1. The enrollment of more than 100 patients with the smooth flow of information and biospecimens.
2. Documenting the inadequacy of current definitions of IBC and the clinical pitfalls delaying diagnosis.

REPORTABLE OUTCOMES

1. Abstracts and presentations in two national breast cancer meetings (San Antonio December 2002 and 2003). (Appendix 2)
2. Inclusion of initial findings in a book chapter entitled "Breast Cancer Aggressiveness in Women of African American Descent." (See Reference below and Appendix 3)

CONCLUSIONS

Several important lessons have emerged from this project. First, neither the AJCC criteria for IBC or the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program criteria for IBC are adequate. The AJCC criteria, primarily clinical, are too extreme and miss a significant percentage of cases. The SEER criteria rely on pathologic confirmation of dermal lymphatic involvement, which is not seen in most IBC patterns. In addition, physician sensitivity to early IBC is inadequate. The high frequency of negative mammograms, the reliance on extensive use of antibiotics and delay of biopsy in a rapidly progressing cancer, and the common belief that a painful breast in a young woman "can't possibly be cancer" are examples of poor medical practice. Continued collection of data and publication in clinical and research oriented journals will hopefully lead to improved method of control.

REFERENCES

Levine P, Veneroso C. "Cancer Aggressiveness in Women of African American Descent" in Eds. Williams C, Falkson C, Olopade O. Breast Cancer in Women of African Descent. In Press.

APPENDICES
Questionnaire (Appendix 1)
San Antonio Abstract (Appendix 2)
Cancer Aggressiveness in Women of African American Descent (Appendix 3)

Pt ID# GWUIBC___   Date of Interview_____

_____

QUESTIONNAIRE

THE ESTABLISHMENT OF AN INFLAMMATORY BREAST CANCER REGISTRY AND BIOSPECIMEN REPOSITORY, IRB# 030105ER

INTRODUCTION: During this interview, I will ask you some questions about yourself, your family, and places where you have lived. Some questions may ask you for sensitive information. I want to remind you that all of your answers will be kept strictly confidential. The information you and others provide is very important to this study.

1a. What is your date of birth?

/___/___/   /___/___/   /___/___/___/___/
(MONTH)   (DAY)   (YEAR)

1b. a- What is current weight?

/___/___/___/   /___/
   (WEIGHT)   pounds=1, kilograms =2, stones=3
b-What was your weight at the time diagnosis?

/___/___/___/   /___/
   (WEIGHT)   pounds=1, kilograms =2, stones=3

1c. What is your height?
/___/   /___/___/
feet   inches

Fill in for the first primary or if patient only had one primary (If only one, fill in 1d – 1m below, and then skip to Q2)
1d. When were you diagnosed with breast cancer ? (Just fill in month and year if you do not remember the day) (Fill in for first primary.)

/___/___/   /___/___/   /___/___/___/___/
(MONTH)   (DAY)   (YEAR)

1e. When did you first notice symptoms?

/___/___/   /___/___/   /___/___/___/___/
(MONTH)   (DAY)   (YEAR)

1ee. How did you first know that there was a problem?
    patient felt a lump   1
    patient noticed something different about breast   2 Describe_____
    doctor felt a lump   3
    lump was found on a mammogram or sonogram   4
    patient noticed something different on skin, such as a
                        growth   5 Describe_____
                        open wound   6
                        discharge   7
                        brown area   8
                        other   9

1f. Did you notice any of the following? (state the percentage of breast affected for each below)

    redness _____ warmth _____   edema ____

    dimpling of the skin like the skin of an orange _____

1g. How quickly did the symptoms appear?

            days /___/___/   weeks /___/___/   months /___/___/

1h. Before you were told that you had inflammatory breast cancer, were you told that your breast
    problem was an infection of the breast?

            YES 1
            NO 5 (THEN GO TO Q1j)

1i. When were you told that?

    /___/___/ /___/___/ /___/___/___/___/___/
    (MONTH)   (DAY)   (YEAR)

1j. Before you were told that you had inflammatory breast cancer, were you told that your breast
    problem was something other than an infection of the breast??
            YES 1
            NO 5 (THEN GO TO Q1l)

_____

1k. What was it that you were told?

_____

1l. Describe other information that led to the diagnosis.

_____

_____

_____

Second Primary

1m. When were you diagnosed with breast cancer ? (Just fill in month and year if you do not remember the day) (Fill in for **second** primary.)

/____/____/   /____/____/   /____/____/____/____/
(MONTH)   (DAY)   (YEAR)

1n. When did you first notice symptoms?

/____/____/   /____/____/   /____/____/____/____/
(MONTH)   (DAY)   (YEAR)

1o. How did you first know that there was a problem?
      patient felt a lump   1
      patient noticed something different about breast   2 Describe _____
      doctor felt a lump   3
      was found on a mammogram or sonogram   4
      patient noticed something different on skin, such as a
                                      growth   5 Describe_____
                                      open wound   6
                                      discharge   7
                                      brown area   8

1p. How quickly did the symptoms appear?

      days /___/___/   weeks /___/___/   months /___/___/

1q. Did you notice any of the following? (state the percentage of breast affected for each below)

      redness _____ warmth _____   edema _____

      dimpling of the skin like the skin of an orange _____

6.26.02   3

2a. Were you born in the United States or outside the United States?

inside the United States   1   _____   _____   _____
   (THEN GO TO Q2c)   (CITY)   (STATE)   (COUNTY)
outside the United States 2   (THEN GO TO Q2b)
don=t know   99 (THEN GO TO Q2c)

2b1. If born outside the United States, where were you born?

CANADA	01
MEXICO	02
CENTRAL AMERICAN (HONDURAS, COSTA RICA, GUATEMALA, PANAMA, BELIZE)	03
SOUTH AMERICA	04
INDIA/PAKISTAN/SRI LANKA	05
CHINA	06
KOREA	07
VIETNAM	08
OTHER ASIAN	09
EUROPE/RUSSIA	10
OTHER (specify) _____	11

2b2. How long have you lived in the United States?
    /____/____/ number of years

Resume

2c. Where was your mother born? _____

2d. Where was your father born? _____

2i. Did your family live on a farm at the time you were born?
    YES 1
    NO 5

2j. What do you consider to be your race or ethnic group? If you belong to more than one group, please tell me all the groups you belong to.

WHITE	01
BLACK, AFRICAN AMERICAN, OR AFRICAN ANCESTRY	02

NATIVE AMERICAN OR INDIGENOUS PEOPLE	03
ALASKAN NATIVE	04
CHINESE, JAPANESE, KOREAN, VIETNAMESE	05
PACIFIC ISLANDER	06
Other (SPECIFY: _____)	07

B. ETHNIC GROUP

EUROPEAN/AMERICAN	01
LATINO/LATINA OR HISPANIC (NOT INCLUDING EUROPEAN SPANISH OR PORTUGUESE)	02
ASIAN INDIAN, PAKISTANI, SRI LANKAN	03
MALAYSIAN	04
FILIPINO	05
Other (SPECIFY: _____)	07

3a. Were you working when you or someone else, such as, a doctor, noticed your first symptoms of breast cancer?

> YES 1
> NO 5

3b. State the job that you had. If you were not working, state what you were doing at that time and answer question 3c for month and year you started doing it.

_____
        (JOB)

3c. What was the month and year when you started working at this job?

/____/____/   /____/____/____/____/
(MONTH)   (YEAR)

3d. Are you currently working at this job?

> YES 1 (THEN GO TO Q3f)
> NO 5

3e. What was the month and year when you stopped working at this job?

____/____/   /____/____/____/____/
MONTH)   (YEAR)

Resume

3f. What were your activities and duties on this job?

_____
      (ACTIVITIES AND DUTIES)

_____

3g. What materials and chemicals did you use or were exposed to on this job? NONE 99

_____

(MATERIALS AND CHEMICALS – including chemicals associated with office work , e.g. carbonless copy paper)

3h. Which term best describes the organization where you work(s/ed) at this job? Would you say it (is/was) a:

business	1
industry	2
government	3
educational institution	4
non-profit or charitable organization	5
something else? OTHER (SPECIFY) 6	_____

(PROBE: What (does/did) the organization do? What products does it produce? What are its activities? What services does it provide?)

4a. Have you had a job in which you were exposed to chemicals on the job?

         YES 1
         NO 5 (THEN GO TO Q5a)

4b. State the jobs and the dates you worked.

(1a) _____   _____
        (JOB)   (CHEMICALS EXPOSED TO - including chemicals
                                   associated with office work , e.g. carbonless copy paper)

(1b) /____/____/ /____/____/____/____/   /____/____//____/____/____/____/
      (MONTH) (YEAR) STARTED   (MONTH) (YEAR) STOPPED

(2a) _____   _____
        (JOB)   (CHEMICALS EXPOSED TO)

(2b) /____/____/ /____/____/____/____/   /____/____//____/____/____/____/
      (MONTH) (YEAR) STARTED   (MONTH) (YEAR) STOPPED

(3a) _____   _____

_____
        (JOB)   (CHEMICALS EXPOSED TO)

(3b) /___/___/ /___/___/___/___/   /___/___//___/___/___/___/
     (MONTH) (YEAR) STARTED   (MONTH) (YEAR) STOPPED

(4a) _____   _____
        (JOB)   (CHEMICALS EXPOSED TO)

(4b) /___/___/ /___/___/___/___/   /___/___//___/___/___/___/
     (MONTH) (YEAR) STARTED   (MONTH) (YEAR) STOPPED

(5a) _____   _____
        (JOB)   (CHEMICALS EXPOSED TO)

(5b) /___/___/ /___/___/___/___/   /___/___//___/___/___/___/
     (MONTH) (YEAR) STARTED   (MONTH) (YEAR) STOPPED

PROBE: What (does/did) the organization do? What products does it produce? What are its activities? What services does it provide?
IF PERSON WORKED ADDITIONAL JOBS WHERE PATIENT WAS EXPOSED TO CHEMICALS, USE CONTINUATION SHEET-4.

Resume
INTRODUCTION: The next several questions ask about your personal medical history. Let=s start with questions about your menstrual cycle.

5a. How old were you when you had your first (menstrual/monthly) period?
         /___/___/
         AGE
         NEVER HAD A PERIOD 99 (THEN GO TO Q6a)

5b. Do you still have your monthly periods?
       YES 1 (THEN GO TO Q6a)
       NO 5
5c. Were you having monthly periods when you were diagnosed with breast cancer?
(Women who are on hormone replacement therapy still have their periods. Try to find out when their periods stopped before they took hormone replacement therapy. What we are trying to get here is the date the patient started menopause)

      YES 1

_____
      NO 5

5d. What was the month and year when you had your last monthly period?
(Again we are looking for the date of the beginning of menopause)
/___/___/   /___/___//___/___/
(MONTH)   (YEAR)

5e. Why did your monthly periods stop? Was it because of:

pregnancy or nursing	1
the change of life or menopause	2
surgery	3
medicine (SPECIFY)	4 _____
radiation	5
chemotherapy	6
another reason? (SPECIFY)	8 _____

Resume

6a. Have you ever had your uterus removed?
      YES 1
      NO 5 (THEN GO TO Q7a)

6b. What was the month and year when you had your uterus removed?

/___/___/   /___/___//___/___/
(MONTH)   (YEAR)

Resume

7a. Have you ever had one or both of your ovaries removed?
      ONE   1
      BOTH 2
      NONE 5 (THEN GO TO Q7c)

7b. What was the month and year when you had your ovary(ies) removed?

/___/___/   /___/___//___/___/   /___/___/   /___/___//___/___/
(MONTH)   (YEAR)   (MONTH)   (YEAR)

7c. Are you a DES baby?
      YES 1
      NO 5

7d. Were you ever given DES?
      YES 1
      NO 5 (THEN GO TO Q8a)

_____

7e. If so, when and for how long?

Beginning date

/___/___/   /___/___//___/___/
(MONTH)   (YEAR)

Ending date

/___/___/   /___/___//___/___/
(MONTH)   (YEAR)

Resume

INTRODUCTION: The next questions ask about your pregnancy history. This includes live births, stillbirths, miscarriages, abortions, and tubal, molar, and other ectopic pregnancies.

8a. On or before your date of diagnosis, were you ever pregnant?
       YES 1
       NO 5 (THEN GO TO Q9a)

8b. Before your date of diagnosis, how many times had you been pregnant? Be sure to count your current pregnancy if you were pregnant when you were diagnosed, and include all pregnancies even if they did not result in a live birth, even if it lasted for a few weeks.
       /____/____/
       # TIMES

8c. How old were you when you were pregnant for the first time even if that pregnancy did not result in a birth?

       /____/____/ AGE

	8d. Date of pregnancy	8e. What was the outcome of your pregnancy?	8f. What was the date of delivery or termination of pregnancy?	8g. If Q8e=1 or 2, Did you breast-feed (any of this/these babies?	8h. How long did you breast-feed each baby?	8i. How long were you pregnant? (for abortions, miscarriages, tubal pregnancies)
1ST	/__/__/ MONTH /__/__/__/__/ YEAR	LIVE SINGLE BIRTH 1 MULTIPLE BIRTHS, 1 or more alive 2 MULTIPLE BIRTHS, 0 alive 3 STILLBIRTH 4 MISCARRIAGE 5 INDUCED ABORTION 6 ECTOPIC OR TUBAL 7	/__/__/ MONTH /__/__/__/__/ YEAR	YES 1 NO 5	/__/__/ # WEEKS 1 MONTHS 2	/__/__/ # WEEKS 1 MONTHS 2
2ND	/__/__/ MONTH /__/__/__/__/ YEAR	LIVE SINGLE BIRTH 1 MULTIPLE BIRTHS, 1 or more alive 2 MULTIPLE BIRTHS, 0 alive 3 STILLBIRTH 4 MISCARRIAGE 5 INDUCED ABORTION 6 ECTOPIC OR TUBAL 7	/__/__/ MONTH /__/__/__/__/ YEAR	YES 1 NO 5	/__/__/ # WEEKS 1 MONTHS 2	/__/__/ # WEEKS 1 MONTHS 2
3RD	/__/__/ MONTH /__/__/__/__/ YEAR	LIVE SINGLE BIRTH 1 MULTIPLE BIRTHS, 1 or more alive 2 MULTIPLE BIRTHS, 0 alive 3 STILLBIRTH 4 MISCARRIAGE 5 INDUCED ABORTION 6 ECTOPIC OR TUBAL 7	/__/__/ MONTH /__/__/__/__/ YEAR	YES 1 NO 5	/__/__/ # WEEKS 1 MONTHS 2	/__/__/ # WEEKS 1 MONTHS 2

4TH	/__/__/ MONTH /__/__/__/__/ YEAR	LIVE SINGLE BIRTH 1 MULTIPLE BIRTHS, 1 or more alive 2 MULTIPLE BIRTHS, 0 alive 3 STILLBIRTH 4 MISCARRIAGE 5 INDUCED ABORTION 6 ECTOPIC OR TUBAL 7	/__/__/ MONTH /__/__/__/__/ YEAR	YES 1 NO 5	/___/___/ # WEEKS 1 MONTHS 2	/___/___/ # WEEKS 1 MONTHS 2
5TH	/__/__/ MONTH /__/__/__/__/ YEAR	LIVE SINGLE BIRTH 1 MULTIPLE BIRTHS, 1 or more alive 2 MULTIPLE BIRTHS, 0 alive 3 STILLBIRTH 4 MISCARRIAGE 5 INDUCED ABORTION 6 ECTOPIC OR TUBAL 7	/__/__/ MONTH /__/__/__/__/ YEAR	YES 1 NO 5	/___/___/ # WEEKS 1 MONTHS 2	/___/___/ # WEEKS 1 MONTHS 2

IF PERSON HAD MORE THAN FIVE PREGNANCIES, USE CONTINUATION SHEET-8.

INTRODUCTION: The next questions ask about your use of hormones.

Resume

9a. Have your ever used or are you currently using oral contraception (birth control pills) for any reason, including the regulation of your periods?

       YES 1

       NO 5 (THEN GO TO Q10a)

9b. How old were you when you first used oral contraceptives?

       /____/____/   /____/____/ /____/____//____/____/

       AGE   (MONTH)   (YEAR)

	9c. Name the brand of oral contraceptives used?	9d. What was the dosage?	9e. How many times per week or month did you take the drug?	9f. When did you first use this brand?	9g. When did you stop using this brand?	9h. Did you take this drug consistently during this time?
1ST	_____ name of brand	_____ dosage	/__/__/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/__/__/ (MONTH) /__/__//__/__/ (YEAR)	/__/__/ (MONTH) /__/__//__/__/ (YEAR)	YES 1 NO 5

2ND			/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	YES 1 NO 5
	_____ name of brand	____ dosage				
3RD			/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	YES 1 NO 5
	_____ name of brand	____ dosage				

IF PERSON USED ORAL CONTRACEPTIVES MORE TIMES, USE CONTINUATION SHEET-9.

9i. Are you still taking oral contraceptives?
    YES 1 (THEN GO TO Q9l)
    NO 5

9j. How old were you when you stopped using oral contraceptives?
    /____/____/   /____/____/ /____/____//____/____/
    AGE   (MONTH)   (YEAR)

9k. Approximately how many years did you take oral contraceptives?
    /____/____/
    NO. of YEARS

9l. Were you using oral contraceptives when you were diagnosed with breast cancer?
    YES 1
    NO 5 (GO TO Q10a)

9m. If yes, what was the name of the brand?   _____

10a. Have you ever taken or are you currently taking hormone replacement therapy (hormones for relief of menopausal symptoms or hormones after menopause)?
    YES 1
    NO 5 (THEN GO TO Q11a)

10b. How old were you when you first used took hormone replacement therapy?
    /____/____/   /____/____/ /____/____//____/____/
    AGE   (MONTH)   (YEAR)

	10c. Name the brand of hormone medication used. Use the number found next to the brands listed below	10d. What was the dosage?	10e. How many times per week or month did you take it?	10f. When did you first use this brand?	10g. When did you stop using this brand?	10h. Did you take this drug consistently during this time?	10i. Did you use this hormone in combination with one of the other hormones you listed
currently using	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/___//___/___/ (YEAR)		YES 1 NO 5	YES 1 NO 5 _____ name of hormone
1ST	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	YES 1 NO 5	YES 1 NO 5 _____ name of hormone
2ND	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	YES 1 NO 5	YES 1 NO 5 _____ name of hormone
3RD	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	/___/___/ (MONTH) /___/___//___/___/ (YEAR)	YES 1 NO 5	YES 1 NO 5 _____ name of hormone

IF PERSON USED HORMONES MORE TIMES, USE CONTINUATION SHEET-11.

HORMONE MEDICATIONS*

1 Amen	14 Estratest	27 Norlutin
2 Amnestrogen	15 Estrocon	28 Nor-Q-D
3 Aygestin	16 Estrogen	29 Ogen
4 Conjugated estrogen	17 Estrovis	30 Ortho-Est
5 Curretab	18 Evex	31 PMB
6 Cycrin	19 Gynetone	32 Premarin
7 Delalutin	20 Gynorest	33 Prempro
8 Depo-provera (DMPA)	21 Hormonin	34 Premphase
9 DES (Diethylstilbestrol)	22 Mediatric	35 Progesterone
10 Estinyl	23 Medroxyprogesterone (MPA)	36 Provera
11 Estrace	24 Menest	37 Provest
12 Estraderm	25 Menrium	38 SK-Estrogen
13 Estratab	26 Norlutate	39 Stilbestrol
		40 Tace

41 Zeste

Other hormone (SPECIFY) _____

*Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services or the Public Health Service.

10i. Are you still taking hormone replacement therapy?
      YES 1(GO TO Q10k)
      NO 5
10j. How old were you when you stopped hormone replacement therapy?
      /____/____/   /____/____/ /____/____//____/____/
      AGE   (MONTH)   (YEAR)

10h. Approximately how many years did you take hormone replacement therapy?
      /____/____/
      NO. of YEARS
Resume
10k. Were you taking hormone replacement therapy when you were diagnosed with breast cancer?
      YES 1
      NO 5 (GO TO Q11a)

10l. If yes, what was the name of the brand (Use the number found next to brands listed above)?

      _____

      name of brand
Resume

_____

11a. Have you ever taken any fertility drugs or hormones to become pregnant?

      YES 1
      NO 5 (GO TO Q12)

11b. How old were you when you took these drugs or hormones?

      /____/____/   /____/____/ /____/____//____/____/
      AGE   (MONTH)   (YEAR)

	11c. Name the brand of drug used. (Use the number found next to the brands listed below.)	11d. What was the dosage?	11e. How many times per week or month did you take the drug?	11f. When did you first use this brand?	11g. When did you stop using this brand?	11h. Did you take this drug consistently during this time?

currently using	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/__//___/___/ (YEAR)		YES 1 NO 5
1ST	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/__//___/___/ (YEAR)	/___/___/ (MONTH) /___/__//___/___/ (YEAR)	YES 1 NO 5
2ND	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/__//___/___/ (YEAR)	/___/___/ (MONTH) /___/__//___/___/ (YEAR)	YES 1 NO 5
3RD	_____ name of brand	_____ dosage	/___/___/ NO. OF TIMES PER WEEK 1 PER MONTH 2	/___/___/ (MONTH) /___/__//___/___/ (YEAR)	/___/___/ (MONTH) /___/__//___/___/ (YEAR)	YES 1 NO 5

IF PERSON USED FERTILITY DRUGS MORE TIMES, USE CONTINUATION SHEET-11.

Medications To Help You Become Pregnant

1 Clomid
2 Clomiphene Citrate
3 Danazol
4 Danocrine
5 HCG
6 Lupron Depot
7 Milophene
8 Nolvadex (Tamoxifen)
9 Pergonal
10 Serophene
11 Synarel Nasal Solution
11 Other (SPECIFY) _____

*Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services or the Public Health Service.

11i. Are you still taking these drugs?

　　　YES 1 (GO TO Q11k)
　　　NO 5

11j. How old were you when you stopped taking these drugs?

　　　/___/___/   /___/___/ /___/___//___/___/

_____
　　　　AGE　　　　　　　　(MONTH)　　(YEAR)

11h. Approximately how many years did you take these drugs?

/____/____/
NO. of YEARS

Resume
11k. Were you taking these drugs when you were diagnosed with breast cancer?
　　　　YES 1
　　　　NO 5

Resume
INTRODUCTION: The next questions ask about the health of your <u>blood</u> relatives. I am only interested in your relatives who are related by blood. Do not include adopted or foster relatives.
12a. Are you adopted?
　　　　YES 1
　　　　NO 5
12b. How many blood sisters do you or did you have? /____/____/

12c. How many blood brothers do you or did you have?   /____/____/

13a. Have you ever had a blood relative diagnosed with breast cancer?
　　　　YES 1
　　　　NO 5 (GO TO Q14a)

13b. Relation to you mother 1 daughter 2 sister 3 half-sister 4 maternal aunt 5 paternal aunt 6 female cousin 7 maternal grandmother 8 paternal grandmother 9 male cousin 10 father 11 son 12 brother 13 other 14	13c. Is your relative alive now?	13d. How old is your relative now or was she/he, when she/he died?	13e. How old was she/he when the breast cancer was diagnosed?	13f. How many breasts were involved?
/_____/ relation	YES 1 NO 5	/__/__/ age	/__/__/ age	one breast 1 both breasts 2
/_____/ relation	YES 1 NO 5	/__/__/ age	/__/__/ age	one breast 1 both breasts 2
/_____/ relation	YES 1 NO 5	/__/__/ age	/__/__/ age	one breast 1 both breasts 2

14. Resume

INTRODUCTION: Now I=m going to ask about places where you lived. State your current residence , your residence at the time of your diagnosis, and any other residences where you were exposed to any of the items listed under question 14e **before** your diagnosis.

14a. What is or was your residence at time of diagnosis, followed by the residences at which you were exposed to any of the items in question 4E? Do not put down house number, only the name of the street.		14b. How old were you when you moved there?	14c. How old were you when you moved away from there?	14d. What were the sources of drinking water at this address?
				  Municipal public water
				    supply 1
				  Private well 2
				  Community well 3
				  Rainwater/cistern 4
				  River/lake/pond 5
				  Spring water 6
				  Bottled water 7
				  Filtered water 8
				Below specify all that apply using the above codes.
					14e. Did you live within 1/2 mile of a:?
					  Dump or landfill 1
					  Hazardous waste site 2
					  Airport 3
					  Farm 4
					  Nursery or greenhouse 5
					  Golf course 6
					  Railroad track used by trains 7
					  Gas station (close enough so that exposed to fumes a lot) 8
					  Medical incinerator 9
					  Quarry 10
					  Factory or industrial plant 11
					(note: 1/2 mile = 6 blocks)
					Specify all that apply below

WHEN DIAG-NOSED	_____ STREET APT _____ COUNTY _____ CITY, TOWN _____ STATE ZIP CODE	/__/__/ AGE	/__/__/ AGE	_____ (1,2,3,4,5,6) _____ Specify Other	_____ (1,2,3,4,5,6,7,8,9,10,11)
NEXT	_____ STREET APT _____ COUNTY _____ CITY, TOWN _____S TATE ZIP CODE	/__/__/ AGE	/__/__/ AGE	_____ (1,2,3,4,5,6) _____ Specify Other	_____ (1,2,3,4,5,6,7,8,9,10,11)

NEXT	STREET APT COUNTY CITY, TOWN STATE ZIP CODE	/__/__/ AGE	/__/__/ AGE	(1,2,3,4,5,6) Specify Other	(1,2,3,4,5,6,7,8,9,10,11)
NEXT	STREET APT COUNTY CITY, TOWN STATE ZIP CODE	/__/__/ AGE	/__/__/ AGE	(1,2,3,4,5,6) Specify Other	(1,2,3,4,5,6,7,8,9,10,11)
NEXT	STREET APT COUNTY CITY, TOWN STATE ZIP CODE	/__/__/ AGE	/__/__/ AGE	(1,2,3,4,5,6) Specify Other	(1,2,3,4,5,6,7,8,9,10,11)

IF HAD MORE RESIDENCES, USE CONTINUATION SHEET-16.

INTRODUCTION: The next questions ask you about work or exposures to agriculture.

15a. Have you ever worked on a farm or in agriculture?
      YES 1
      NO 5

15b. Have you ever lived on a farm?
      YES 1
      NO 5 (GO TO Q15d)

15c. For how many total years did you live on a farm?
      LESS THAN 1 YEAR...................1
      1 TO 5 YEARS..........................2
      6 TO 10 YEARS........................3

_____
             MORE THAN 10 YEARS…………..4

15d. In any of the places you lived, has any person living with you (such as a family member) worked on a farm or in agriculture **while they were living with you?**
        YES 1
        NO 5 (GO TO Q15g)

15e. Did that person work on a farm or in agriculture when you were diagnosed with breast cancer?
        YES 1
        NO 5

15f. What crop or crops did that person or you farm? Enter 99 for any information you do not remember.

Name of Crop	Type of Work	Relationship to you	What Year(s)	City	State	County

15g, Have you ever lived directly next to a field that was growing crops?
        YES 1
        NO 5 (GO TO Q16)

15h. What crops were growing? Enter 99 for any information you do not remember.

Name of Crop			What Year(s)	City	State	County

16a. During any time in your life, have you (or anyone you lived with **while living with you**) used or been exposed to the following chemicals **before** your date of diagnosis with breast cancer?

6.26.02   20

YES   1   don=t know 99 (GO TO Q17a)
NO   5 (GO TO Q17a)

16b. For each chemical exposed to, circle the number next to the chemical and answer the following: Enter 99 for any information you do not remember.

Chemical		Work Type	Relationship to you	What Year(s)	City	State	County
Atrazine	1						
Aarex	2						
Gesparin	3						
G - 30027	4						
Malermais	5						
Simazine	6						
Simadex	7						
Cekusima	8						
Framed	9						
Totazina	10						
Cyanazine	11						
SD - 15418	12						
WL 19805	13						

17a. Do you or did you (or anyone else) put herbicides (chemicals) regularly on your lawn, garden, outdoor plants and trees, indoor plants **before you were diagnosed** with breast cancer? Examples of reasons for using herbicides are: weeds, diseases, mildew, scale, rot.
        YES   1   don't know 99 (GO TO Q18a)
        NO   5 (GO TO Q18a)

_____

17b. Name the herbicide(s) used.

17b. Name of herbicide	17c. How often did you use it?	17d. What years?	17e. Who applied the treatments? you 1 lawn service 2 gardener 3 exterminator 4 someone else 5
_____ name of brand	/___/___/ # of times WEEKS 1 MONTHS 2 YEAR 3		
_____ name of brand	/___/___/ # of times WEEKS 1 MONTHS 2 YEAR 3		
_____ name of brand	/___/___/ # of times WEEKS 1 MONTHS 2 YEAR 3		

18a. Do you or did you (or anyone else) spray your house regularly with pesticides **before you were diagnosed** with breast cancer? Examples of pests that pesticides would be used against are: flies, mosquitoes, bees, wasps, hornets, moths, ants, roaches, silverfish, spiders, mice, rats, squirrels, gophers, moles, bats, fleas, ticks, termites, carpenters ants.

        YES   1   DON'T KNOW 99 (GO TO Q18g)
        NO   5   (GO TO Q18g)

18b. Name the pesticide(s) used . (including Black Flag, Raid, etc.)

18b. Name of pesticide	18c. How often did you use it?	18d. What years?	18e. Who applied the treatments? you 1 lawn service 2 gardener 3 exterminator 4 someone else 5
_____ name of brand	/___/___/ # of times WEEKS 1 MONTHS 2 YEAR 3		

_____ name of brand	/___/___/ # of times	WEEKS 1 MONTHS 2 YEAR 3	
_____ name of brand	/___/___/ # of times	WEEKS 1 MONTHS 2 YEAR 3	

18f. Were you spraying your house regularly within the five years **before** you were diagnosed with breast cancer?

     YES   1   don=t know   99
     NO   5

18g. Was the office where you held your last job before diagnosed with breast cancer sprayed with pesticides regularly?

     YES   1   don't know   99
     NO   5 (GO TO Q19a)

18h. How often?

     /___/___/   per   week   1
     # TIMES   month   2
                       year   3
                       don=t know 99

18i. Did the community ever spray you or your home for insects such as gypsy moths, Mediterranean fruit flies, mosquitoes, West Nile virus **before you were diagnosed** with breast cancer?

     YES   1   don=t know   99
     NO   5

18j. Which pest did your community spray for? (mark all that apply)

HOW OFTEN # times   per week 01 --- per month 02 --- per year 03 ---- don't know 99

gypsy moths	1	what years	from_____ to _____	/__/__/	per _____
Mediterranean fruit flies	2	what years	from_____ to _____	/__/__/	per _____
mosquitoes	3	what years	from_____ to _____	/__/__/	per _____
West Nile virus	4	what years	from_____ to _____	/__/__/	per _____
Other	5	what years	from_____ to _____	/__/__/	per _____
Specify _____					

Resume. INTRODUCTION: The next questions ask you about certain diseases or medical conditions you may have had **before** your date of diagnosis of breast cancer.

MEDICAL CONDITION	19a. Before your date of diagnosis, did a doctor or other health provider ever tell you that you had this medical condition?	19b. In what year were you told that you had this medical condition?	19c. Did you ever have treatments for this medical condition including hospitalization, surgery, or medication?
Thyroid condition (not cancer): (select one from below) Hashimoto=s disease 1 Grave=s disease 2 Hyperactive (overactive) 3 Hypoactive (underactive) 4 Goiter 5 Nodules 6 Other 7 Don=t know 99	YES 1 NO 5	/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Breast cancer	YES 1 NO 5	/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Ovarian cancer	YES 1 NO 5	/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Cervical cancer	YES 1 NO 5	/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5

Uterine cancer	YES 1 NO 5	/__/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Another cancer of the female genitals. Please specify _____	YES 1 NO 5	/__/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Colon cancer	YES 1 NO 5	/__/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Melanoma cancer	YES 1 NO 5	/__/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Lung cancer	YES 1 NO 5	/__/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Thyroid cancer	YES 1 NO 5	/__/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5
Other type of cancer. Please specify _____	YES 1 NO 5	/__/__/__/__/ (YEAR)	medication 1 hospitalization 2 surgery 3 radiation 4 chemo 5

19d. Have you ever received radiation in the treatment of a condition or disease that you had other than any radiation you had for your breast cancer **before** you were diagnosed with breast cancer?
        YES   1
        NO   5 (GO TO Q19f)

19e. What years? /_____/

19f. Have you ever been exposed to sustained periods of radiation **before** you were diagnosed with breast cancer (do not count normal numbers of mammograms, chest x-rays, dental x-rays, or other diagnostic x-rays – Probe about x-ray treatments when the patient was younger, such as for acne, etc) ?
        YES   1
        NO   5 (GO TO Q20a)
19g. What years? /_____/

20a. Did you ever smoke **regularly before** you were diagnosed with breast cancer?
        YES   1
        NO   5 (GO TO Q21a)

20b. How many years did you smoke? _____ what years _____

20c. How many packs a day did you average? _____

21a. Did you ever drink alcohol **regularly before** you were diagnosed with breast cancer?
        YES   1
        NO   5 (GO TO Q22)

21b. type of alcohol	21c. number of drinks	21d. per day 1 per week 2 per month 3 per year 4	21e. what years
wine			
beer			
hard liquor			

22a. Did you take any **megadoses** of vitamins, herbs, or any other supplements including any that you may take for the relief of menopausal symptoms or menstrual pain **before** diagnosis?
        YES   1
        NO   5 (GO TO Q23)

22b. name of vitamin, herb, or supplement	22c. number of pills	22d. per day 1 per week 2 per month 3 per year 4	22e. what years

23a. Did you eat many soy products, such as soy milk, tempeh, soy nuts, tofu, soybeans, soy flour, soy flakes, soy protein, soy sprouts, miso, soy cheese **before** diagnosis?

        YES   1

        NO   5 (GO TO Q24a)

23b. name of soy product	23c. number of servings	23d. size of serving	23e. per day 1 per week 2 per month 3 per year 4	23f. what years
soy milk				
tofu				
soy nuts				
soy beans				
tempeh				
soy flour				
soy flakes				
soy protein textured				
soy protein not textured				
soy sprouts				
miso				
soy cheese				

24. Have you experienced any significant traumas or stresses within 5 years **prior** to your diagnosis?

                                                                    dates

    A. death of a family member or significant other   _____

    B. change in relationship or spouse   _____

    C. other traumas   _____

24b. Is there anything else you want to tell me about your breast cancer, such as any exposures that you think might be relevant?

_____

25. State the name and address of the doctor who is currently treating you for breast cancer.

26. Initials of interviewer   _____

27. Date of interview   /___/___/ /___/___/ /___/___/

                            month   day   year

[305] The inflammatory breast cancer registry: an approach to standardization.
Levine PH, Sherman M, Veneroso CC. George Washington University School of Public Health and Health Services, Washington, DC; National Cancer Institute, Bethesda, MD

Date/Time: Thursday, December 12, 2002 7:00 AM **Location**:

Session Info. : Poster Session III: Epidemiology and Outreach: Epidemiology (7:00 AM-9:00 AM)

Background: Inflammatory breast cancer (IBC) is a rare highly aggressive form of cancer, which seems to disproportionately affect black women. Although IBC is recognized as a specific clinical entity, diagnostic criteria for IBC are controversial. The purpose of the IBC Registry (IBCR) is to develop a large, centralized and standardized resource of IBC cases that could be used to refine diagnostic criteria and characterize the epidemiological, clinical, pathological and molecular characteristics of these tumors.
Methods: The IBCR is recruiting all patients suspected of having IBC who consent to participating in an interview assessing risk factors and whose tissue blocks are available for laboratory evaluation. Initially, patients are classified according to clinico-pathologic criteria into three groups: (1) clinical presentation typical of IBC with pathologic confirmation; (2) clinical presentation typical of IBC without pathologic confirmation; (3) pathologically defined IBC without typical clinical features. Subgroups will include patients with incomplete criteria according to AJCC definition, e.g. redness, warmth and edema involving less than half the breast, edema (peau d'orange) without redness, etc.
Results: Thus far, we have studied IBC patients in Tunisia, California and the George Washington University Medical Center to establish our data collection system. A preliminary study comparing 45 IBC cases to 22 non-IBC breast cancer controls from Tunisia has recently suggested that IBC is associated with increased microvessel density (McCarthy et al, ASCO, 2001). Additional ongoing work is focusing on whether mouse mammary tumor virus sequences are associated with IBC (Coronel et al, submitted).
Conclusion: The centralized collection of specimens and data in the IBC registry will be made available to investigators throughout the breast cancer research community. It is hoped that this project will lead to molecular characterization of IBC and a more objective classification of IBC patients.

The inflammatory breast cancer registry: preliminary findings from 50 patients.

Paul H. Levine, MD(1) and Ladan Zolfaghari MD (2)   (1) is Environmental Epidemiology Branch, DCEG,NCI (2) is. [1] Epidemiology and Biostatistics, The George Washington University School of Public Health and Health Services, Washington, DC, United States.

Background: Although inflammatory breast cancer (IBC) is recognized as an aggressive form of breast cancer, controversy surrounding diagnostic criteria for these tumors has limited our understanding of the etiology and clinical behavior of IBC. The IBC registry was established to collect standardized information and specimens from IBC patients with the goal of clarifying the etiology and biology of these tumors. **Methods:** Patients with IBC are entered into the Registry if they agree to interviews, evaluation of their medical records and access to pathologic specimens. The first 50 patients were either self-referred through information obtained on the internet (46) or via The George Washington University Medical Center physicians (4). **Results:**Approximately one-third were initially diagnosed as having an infection and received antibiotics for up to five months before the diagnosis of IBC was made. Mammographic findings were variable with most cases not having a discrete identifiable mass. Cases were reported initially at referring institutions as ductal carcinoma (n=47); lobular carcinoma (n=2) and multi-focal colloid carcinoma (n=1). Approximately 45% were ER+. The clinical presentation was extremely varied. Cases were classified into seven subgroups, depending on clinical and pathologic findings.

Forty-nine patients received neoadjuvant chemotherapy, usually including Adriamycin and Cyclophosphamide and usually followed by mastectomy, the timing of the mastectomy depending on the chemotherapy response. Forty-six patients (92%) received radiation therapy post mastectomy. Half of the patients reported an excellent initial response to chemotherapy.

Discussion
Diagnosis of IBC in community practice remains problematic; challenges include lack of clinical experience and failure to adequately consider IBC in young women with painful breasts. Criteria for IBC and tumors with similar clinicopathologic features require re-assessment to achieve better standardization; dissemination of these criteria are needed.

Chapter 13c

BREAST CANCER AGGRESSIVENESS IN WOMEN OF AFRICAN DESCENT

Paul H. Levine MD and Carmela Veneroso, MPH
Tthe George Washington University School of Public Health and Health Services

1.   INTRODUCTION

While the incidence of breast cancer is higher in White women (115.5/100,000) than African-American women (101.5/100,000), the mortality pattern is just the opposite (1). Not only do African-American women have a higher mortality (31.0/100,000) than White women (24.3/100,000) but the mortality rates are falling more rapidly in White women. There are many factors that may contribute to these disparities, such as inequalities in access to healthcare and poverty (2-4), and lower education levels (5). These factors create barriers to health care access contributing to African-Americans being diagnosed at a later stage of disease (6-11). Some studies have shown that socioeconomic factors are associated with a poorer outcome and may account for some of the difference between African-Americans and Whites (12-17). However, even when African-Americans have equal access to medical care, there are still racial differences in outcome (18, 19). In the Jatoi et al.'s 2003 study of breast cancer survival in the U.S. Department of Defense's Healthcare System, an "equal access system", (18) they found, after adjusting for age and stage, that not only was there a disparity in survival between African-American women as compared to Whites, but that this disparity has increased since 1980. Other studies show that factors other than delay in presentation and socio-economic status explain some of the disparity and that African-American women still have poorer survival after controlling for these factors (20-22).

There is increasing evidence that breast cancer is more aggressive in African-Americans and that African-Americans have more biologically aggressive tumors defined by specific markers that are associated with a worse prognosis or worse survival. One marker of aggressive breast cancer on which there is general agreement is tumor grade. Many studies have shown that histologic grade is a statistically significant prognostic factor for disease free survival and overall survival (23-34). Grade is evaluated at time of diagnosis and therefore reflects events occurring in the tumor before diagnosis and treatment. Grade provides measurements of differentiation, nuclear grade, and mitotic count, important parameters in the aggressiveness of the tumor.

Other markers associated with worse prognosis and more aggressive disease are negative hormone receptors (35, 36), aneuploid tumors (37, 38), high s-phase (39, 40) , and increased microvessel density (41). Many studies have shown that a larger percentage of African-American women as compared to white women have these markers (6, 7, 42-56).

One form of breast cancer that offers an excellent opportunity to identify aggressive breast cancer is inflammatory breast cancer (IBC), one of the most aggressive forms of breast malignancies. IBC reportedly comprises only 1-6% of all breast cancer cases but it may constitute up to 10% of breast cancers in African-American women. Some investigators categorize IBC as a subgroup of locally advanced breast cancer (LABC)(57, 58), but as noted by Wolff and Davidson (59) despite the inclusion of IBC in most classifications of LABC, it has a distinct clinical behavior and worse prognosis. As noted below, the importance of chemotherapy as primary treatment for IBC is based on its early dissemination of micrometastases which are more susceptible to destruction before they have a chance to develop resistance.

Analyses of data from Surveillance, Epidemiology, and End Results (SEER) Program (60, 61) document the greater impact of IBC on African-American women than any other racial/ethnic group, but the extent of this impact depends on the case definition. In our earlier report (60), where we analyzed SEER data between 1975 and 1981 involving 56,683 cases of invasive breast cancer in women, (51,030 White, 3,834 Black, and 1,819 other non-White), we concentrated on analysis of data from White patients because of the larger number of cases. In this group, patients were classified as having clinical features of IBC without pathologic confirmation (1,181 patients), pathologic features of IBC without clinical features (38 patients), both clinical and pathologic features of IBC (62 patients), and no evidence of IBC (25,089 patients). Using the broadest definition of IBC (all three IBC groups), 10.1% of African-American women with breast cancer had evidence of IBC as compared to 6.2% in White patients and 5.1% in other non-Caucasians. With the requirement for pathologic confirmation, the percentage dropped to only 0.7% of African-American breast cancer patients having IBC vs. 0.5% in Caucasians (60). In a follow-up study encompassing 1975-1992 (61), there was confirmation that the incidence of IBC in African-American women is significantly higher than White women (1.1 per 100,000 person years as compared to 0.7 per 100,000 person-years), the relatively small number resulting from the exclusion of those cases with only clinical features of IBC (in our earlier study there were 11 times the number of patients with only clinical features as those with pathological evidence of IBC (60)). A second intriguing finding in Chang's study is that the incidence in both African-American and White women doubled between 1975-77 and 1990-92. Whether this represents a true increase in IBC or a greater awareness of the need for skin biopsies in IBC patients to document invasion of the dermal lymphatics remains to be demonstrated. In our experience with the Inflammatory Breast Cancer Registry (IBCR) (62), a recently initiated project designed to obtain uniform clinical and epidemiologic information as well as biospecimens from IBC patients throughout the United States and Canada, we see that a higher proportion of women are getting multiple skin biopsies to document pathologic involvement, and in one cluster of patients in California, the surgeon had to take more than ten biopsies before "pathologic proof" of IBC could be found (Levine, unpublished data).

In this chapter, we will review some of the pertinent studies that have shed light on the problem of aggressiveness and emphasize the emerging data on risk factors for aggressive breast cancer, which actually cross into all racial/ethnic groups and are the target of intensive research in our University.

2. HISTORICAL ASPECTS

A focus on aggressive breast cancer has generally been attributed to an English surgeon, Sir Charles Bell, who noted in 1814 that an enlarged purplish painful breast was a poor prognostic sign (63). Several authors have noted breast cancer associated with pregnancy also tends to be more aggressive with a poor prognosis (64) (65) but this has not been universally accepted (65). Until recently, however, a consistent focus on aggressive breast cancer was not possible because the tools for detecting these cases were not readily available. Only when there were dramatic clinical signs, as with IBC, could a poor survival be predicted. The emphasis on diagnosing IBC as a clinical entity continued when Taylor and Meltzer in 1938 emphasized the clinical manifestations but noted that invasion of the dermal lymphatics should be considered as "pathologic proof" (66). As noted above, this is the approach currently adopted by AJCC (67).

The move towards a pathologic definition began with the 1974 report of Ellis and Teitelbaum (68) based on their examination of skin biopsies in five long term IBC survivors noting that "none of these patients had dermal lymphatic metastases." Further support of IBC as a pathologic entity was provided by Saltzstein (69) who described the opposite end of the spectrum, noting dermal lymphatic invasion in four patients with rapid progression of breast cancer but no clinical evidence of IBC. He used the term "clinically occult inflammatory breast cancer," which we identified in the SEER database as Group III and which appears to have a worse prognosis than those with only clinical manifestations (Figure 1) (60) . In 1978, Lucas and Perez-Mesa (70) documented a poor survival in their 58 patients with clinical IBC and 15 patients with "occult" inflammatory cancer, thus indicating that either clinical or pathologic features were sufficient to support a poor prognosis.

In France's Institut Gustav Roussy, Denoix developed a terminology to investigate aggressive breast relying more on the rapidity of tumor growth than any other characteristic (71) . Using the term *"pousée évolutive"* (PEV) to designate rapidly progressing breast cancer, he defined four forms: PEV-0 is a designation given to patients without inflammatory signs and no history of rapid tumor growth; PEV-1 is a designation given to patients who describe rapid tumor growth but who show no inflammatory signs; PEV-2 is a designation given to patients with inflammatory signs involving less than half of the breast; PEV-3 is a designation given to patients with inflammatory signs involving more than half of the breast. PEV-3 would be recognized as inflammatory breast cancer readily by clinicians world-wide. Investigators at the Institut Salah Azaiz in Tunisia noted that 58.5% of the 581 cases of breast cancer seen there between 1969-1974 were PEV positive (PEV-1, PEV-2, or PEV-3); of the 581 cases, 48.5% were PEV-3 (the IBC equivalent) and 10% were PEV-1 and PEV-2. (72). This finding launched a series of studies that have proven to be highly relevant to current studies of IBC in North America. Among the more important findings were the dramatic improvement in survival with neoadjuvant therapy (73, 74), the observation that the risk

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factors for breast cancer aggressiveness differed from those for developing breast cancer (75) (see below), and the indication that there was a higher percentage of patients with evidence for a human breast cancer virus (76). More recently, we examined biopsies from 45 Tunisian patients using molecular techniques and found that microvessel density was significantly higher in those with clinical features of IBC compared to those without (41), indicating increased angiogenesis in the Tunisian IBC patients.

3. THE IMPACT OF AGGRESSIVE BREAST CANCER ON AFRICAN-AMERICAN WOMEN

As discussed above there are many studies that indicate that African-Americans have more aggressive disease (6, 7, 42-57, 60). While data from the SEER program of the National Cancer Institute (NCI) document a worse tumor grade (43), an indicator of more aggressive cancer, and a poorer survival in African-American women, the strongest data for the importance of tumor aggressiveness come from studies of breast cancer in the "equal access" health care system of the military (18, 19). While these studies looked at survival and not directly at tumor aggressiveness, the implication is that all patients in the military had essentially the same treatment for their disease and therefore the poorer survival in African-American women was not due to unequal access to care. Therefore, since many other studies show that African-Americans have tumors that are more biologically aggressive, aggressiveness may be the key factor in the survival difference in the military population. However, not all studies are in agreement. English et al. (77) found that there was no difference in overall survival or survival by stage in a study of 585 African-American and white women treated in their university teaching hospital between 1990 and 1999, despite the fact that the African-American patients were younger, presented with higher-stage tumors, were more often to have positive axillary lymph nodes, were more often to have negative estrogen and progesterone receptors, and were more often premenopausal.

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4. IMPORTANT RESEARCH QUESTIONS IN AFRICAN AMERICAN WOMEN

4.1 What is the relative impact of tumor aggressiveness vs. access to care on mortality rates in African-American women?

At the present time, there are no available data that address the question of the relative impact of tumor aggressiveness vs. access to care on the poorer survival of African-American women with breast cancer. However, the poorer survival of African-American women in "equal access" studies (18, 19), suggest that tumor aggressiveness may have a major impact on African-American women. A number of studies have noted that there is a major impact from access to care, co-morbidities, quality of insurance and different treatment strategies (5, 46) but these issues are likely to be exacerbated by tumor aggressiveness. More recently we have investigated this issue on a nationwide basis using SEER data comparing tumor grade in African-American and Caucasian women by stage at presentation (43). We found that regardless of disease stage, the histological grade of the tumor was significantly higher in the African-American women. There may well be better markers of aggressiveness, such as molecular markers, but tumor grade is useful since it is determined at the time of diagnosis before treatment. While lymph node involvement is an important prognostic indicator, it does not distinguish between slow growing tumors that have been present for a considerable time and rapidly growing tumors of recent onset.

4.2 What are the risk factors for breast cancer aggressiveness

There is evidence that the development of aggressive breast cancer depends heavily more on environment than genetics (see below). International comparisons of aggressive breast cancer are difficult due to differences in Registry procedures and case definitions. However, one source of data comes from the study of aggressive breast cancer cases at the Institut Salah Azaiz in Tunisia (as discussed above) where 48.5% of all breast cancer patients presented as PEV-3 (the equivalent of IBC), compared to the United States where 1-6 % of all breast cancer cases patients are reported as IBC. Within Tunisia the proportion of PEV positive patients was more in the rural than urban population and there was a suggestion that pregnancy at an early age was a risk factor (75). Other studies discussed below also seem to indicate an environmental influence.
While the etiology of breast cancer has been studied extensively and many risk factors have been established, risk factors for aggressive breast cancer have not been well studied. The few studies that have been done have looked at these factors in relation to survival and have yielded contradictory results. These contradictory results may be due to the difficulty in controlling for treatment that has an impact on survival. There have been even fewer studies that have looked at these factors in relation to the aggressiveness of the tumor. In some of these survival and aggressiveness studies, factors that are known to be protective of developing breast cancer have been associated with worse survival and/or a more aggressive form of breast cancer. Mourali et al.(75) found that late age at menarche, an established protective factor associated with a decreased risk of developing breast cancer (78) was associated with an increased risk of developing aggressive breast

cancer. Korzeniowski et al.(79) found that reproductive factors known to decrease risk, specifically late menarche and parity, were associated with an adverse impact on survival. Kroman et al.(80) found that at first birth, a very well established risk factor for decreased risk for developing breast cancer, was associated with a worse prognosis. This finding is compatible with the observation that 14/15 Tunisian women who had their first child under the age of 18 were PEV positive (75).

Other risk factors that have been associated with more aggressive tumors are young age at diagnosis, oral contraceptive use (OC), exposure to organochlorines, and obesity (see below).

4.1.1 Early Age at First Pregnancy

A number of studies have found that women who had their first child at an early age had a poorer prognosis (75, 80-83). In Schouten et al.'s 1997 study of 866 breast cancer patients, they found that young age at first full-term pregnancy was related to decreased survival (82). In Kroman et al.'s 1998 study of the prognosis of reproductive factors in 10,703 women with primary breast cancer in the Danish Cancer Registry, they found that women who had their first child before the age of 20 had a higher risk of dying than women who had their first child at age 20 and above (80). Supportive evidence was provided by Chang's study on IBC, where it was found that IBC patients were younger at the time of their first live birth than non-inflammatory breast cancer patients and non-breast cancer patients (81). And finally in an early study on pre-menopausal women, Greenberg found that women who were older when they had their first child had a better prognosis (83).

However, some studies have not supported a poorer prognosis for young age at first birth. In Lund's study of breast cancer mortality of 800,814 Norwegian married women, women who had their first birth after age 35 had a 2.6 higher risk of mortality than women who had their first birth before age 20 (84). This discordant study is difficult to explain, but could be due to population differences and some factor associated with late age at first pregnancy. In a Northern Alberta study, age at first birth was not found to have a significant effect on survival but this analysis was performed using age at first birth as a continuous variable; direct comparison of women whose first birth was at less than age 20 was not made with those whose first birth was after age 20 (85).

4.1.2   Young Age at Diagnosis

Many studies have found an association between young age at diagnosis and a poor prognosis (86-97). Some of these studies have shown that patients diagnosed at a young age have more aggressive tumors. In Maggard et al.'s 2003 study (94) of 24,935 invasive breast cancer patients using the SEER database (1992-1998), they found that young breast cancer patients had poorer survival as compared with an older cohort and that the younger women presented at a more advanced stage disease and had more aggressive tumor characteristics, that is, higher grade tumors and more estrogen- and progesterone receptor-negative tumors. Marcus et. al.'s study (95) found that the invasive breast cancer tumors in the younger women were of higher grade and more proliferative. Kollias' study (96) found that patients who were less than 35 years old presented more frequently with high grade tumors. Walker et al. (97) found that women aged under 35 years had a

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significantly high incidence of having poorly differentiated tumors, higher proliferation rates, and a significantly high incidence of p53 protein staining. Bonnier et al. (91) found a higher frequency of high grade and undifferentiated tumors, microscopic lymph-node involvement, and negative hormonal receptor status was observed in patients under 35 years.

4.1.3 Oral contraceptive use

A complex relationship between OC use and breast cancer prognosis has been evident in many of the studies on OC use and prognosis. A number of early studies showed no association with OC use with prognosis (83, 98-100). However, some of these studies were very small and had few users before their first full-term pregnancy. On the other hand, other studies found use of OC was associated with a poorer prognosis although with conflicting results. Some of these studies found that pre-menopausal patients with a history of OC use had larger tumors, more metastases, lower PR and ER receptors, higher S-phase, frequency of aneuploidy, and poorer survival (101-104). And in Brinton's study (105) on oral contraceptive use and breast cancer risk among younger women, they found that OC associations were stronger for more advanced tumors. In contrast, however, some studies found a beneficial effect. A more recent study done by Sauerbrei et al. found no effect on survival and found that OC users had smaller tumors (106). In Vessey's study published in 1983 they found that women who never used OC presented with more advanced tumors; however, only small numbers of cases and controls had prolonged OC use before their first pregnancy (107). The conflicting data regarding the effect of OC use on tumor aggressiveness and survival may the result of the different approaches to evaluating the length of time of OC use.

Other studies also found that the effect of OC use varied, depending on the length of use. A study published in 1994 by Holmberg suggested that short duration of use had a favorable effect on the prognosis (108). Holmberg found that 5-year survival estimates for users of 1-3 years (short-term users) had a significantly better prognosis than never users, while users of four years or more had a non-significant worse prognosis. Yet, in Schonborn's study also published in 1994, they found that long-term use of OC had a significantly increased 5 year survival time, but only significantly for those who used OC for greater than 4 years (109). They also found that long-term OC use increased survival for patients with poor histopathological prognostic factors (number of positive nodes, large tumors, low ER, low PR, histological grade). Of note, was that they found statistical significance on all of the factors except tumor grade. They found that long-term users had a statistically significantly higher number of poorly differentiated tumors, perhaps suggesting an effect of OC use on tumor biology. This poor tumor biology should suggest a worse prognosis. Interestingly, they also found a significant correlation between long-term use and current use. Perhaps this strong correlation of long-term users with current users suggests current OC use (hormonal influences) has an effect on the behavior of the tumor in the subclinical phase. The results may have been different, if they did not include current users. Finally, in a more recent study published in 1997, Schouten et al. looked at the association between oral contraceptive use and survival (82) and found no association with prior use of OCs. However, he did not find a statistically significant increased relative risk of dying for use greater than 5 years.

Other studies looked at the effect of the age at which the woman started her use of OC. A couple of studies showed that survival was worse in women who had started OC use before the age of 20 (102, 110). In Olsson's 1991 study of primary tumor specimens from 72 premenopausal women, they found that amplification of Her-2/neu, which is associated with more aggressive tumors (111, 112), was much more common among OC users who started using OC before the age of 20 (113). He found that no significant associations were found between amplification and the variables of parity, age at first full-term pregnancy, or late abortion, suggesting that the higher rate of Her-2/neu amplification among early oral contraceptive users is an effect of the oral contraceptive use per se rather than of the relative youth of the users. However, Holmberg found no evidence of a worse prognosis for women who used OCs at an early age (108).

4.1.4   Other Risk Factors

Other risk factors that have been associated with more aggressive tumors are exposure to organochlorines and obesity. Although Demers et al. (114) found no relation between organochlorines and the risk of developing breast cancer, they found that some organochlorines and especially p,p'-DDE was associated with breast cancer aggressiveness. Specifically they found a probability of lymph-node invasion among breast cancer cases with increased exposure to 1,1-dichloro-2,2-bis (4-chlorophenyl) ethylene and that p,p'-DDE exposure was associated with a dose-related increased relative risk of exhibiting both lymph-node involvement and a large tumor. Similar associations were noted with beta-hexachlorocyclohexane, oxychlordane, and transnonachlor. Woolcott et al.'s study(115) found that many polychlorinated biphenyls (PCB) were more strongly associated with tumors of poor prognosis, that is tumors which were larger and higher-grade and estrogen receptor negative.

Finally, several studies have found that obesity was associated with a worse prognosis (81, 116, 117). Daling et al. (117) found that the women younger than 45 years of age in the highest quartile of BMI were more likely to be estrogen receptor negative and have a high S-phase fraction, a high histologic grade, a high mitotic cell count, and large tumor size compared with the tumors of women whose BMI was in the first quartile. Relative to the large tumors in women in the lowest BMI quartile, the large tumors in women in the highest BMI quartile were more likely to express markers of high proliferation, indicating they may have grown faster than similar size tumors of the thinnest women. Finally Chang et al. found that high BMI was significantly associated with an increased risk of IBC (81).

4.3   How should aggressive breast cancer and IBC be defined?

There are a number of studies that have investigated racial differences using various markers of aggressiveness and as noted earlier many of those studies looked at the differences in tumor grade. African American women have been observed to have higher grade tumors compared with white women (43, 45, 48, 118). More recently, a study by Henson et al.(43) used SEER registry data from 1992-1999 and looked at the correlation between survival and histological grade, stage of disease, and tumor size for African-American and white women. This study found that for nearly every combination of stage and grade, regardless of age, African-American women presented with

proportionally more Grade III and fewer Grade II tumors. Higher grade was associated with a less favorable 6-year cause specific survival. (The difference was not statistically significant for every combination of grade and stage, but it was observed in 12 of the 13 combinations analyzed).

There have been a number of studies that looked at differences in different markers of aggressiveness between African-American and white female breast cancer patients. Many of these studies have shown that African-American women are more likely to present with estrogen receptor negative tumors (42, 47, 55, 56) and high s-phase (47). Research may not only benefit from better classification of aggressive breast cancer, but also a more acceptable and consistent definition of IBC, the prototype of aggressive breast cancer.

The current definition of IBC continues to be problematic. Not only do individual clinicians differ in their criteria for diagnosis of IBC but national organizations also disagree. The American Joint Committee on Cancer (AJCC) emphasizes the clinical features and states that "Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast (which) should involve the majority of the skin of the breast." "It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. Involvement of the dermal lymphatics alone does not indicate inflammatory carcinoma in the absence of clinical findings"(67). In contrast, the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program defines IBC as a clinical diagnosis verified by biopsy of the tumor and overlying skin (119). The two major reviews of IBC using SEER data (60, 61) note that although a relatively small group, SEER does include cases defined pathologically without any clinical evidence of disease. The implications of these disparate definitions and approaches are considerable and explain notable differences in estimates of the incidence of IBC, even using the same source of data. Our first review of SEER data used cases fitting clinical or pathologic criteria identified between 1975 and 1981 (60). In an updated analysis including patients identified by SEER through 1992, Chang et al. evaluated only women who had pathologically defined IBC because of their concern that the clinical classification could include cases of neglected breast cancer (61). Regardless of whether the criteria are primarily clinical or pathological, it is clear that the prognosis is generally much worse than for any other form of breast cancer (60). Cristofanilli et al. (58) report that IBC patients "usually present with a rapid onset of swelling of the involved breast." They add that "The classic criteria established by Haagenson (120) include diffuse erythema, edema involving more than two-thirds of the breast, peau d'orange, tenderness, induration, warmth, enlargement and diffuseness of the tumor on palpation." While this is indeed the classic definition, more often patients are being diagnosed at a much earlier stage where the redness may be far more limited and there may initially be peau d'orange without erythema or the converse. Waiting until the breast shows the classic findings can seriously diminish the chances of a cure, which is now possible in a significant percentage of patients.

5.   CURRENT RESEARCH.

5.1   Case Definition

The investigation of a disease, whether related to etiology, pathogenesis or control, requires a tight case definition. As discussed above, there is no universally accepted case definition for aggressive breast cancer or for IBC. Investigators often rely on tumor grade but other criteria, such as hormone receptor and Her2-neu status have been used. Similarly, there is disagreement as to the precise case definition of IBC. The AJCC (67), which defines IBC as predominantly a clinical disease involving more than half of the breast, may well be inadequate since the diagnosis is made with far less clinical involvement, and this early diagnosis appears to be appropriate.

In 2001 we initiated the Inflammatory Breast Cancer Registry to describe the variations in the diagnosis of IBC and to attempt to determine if molecular diagnostic tools could be identified to bring some improved classification to a disease defined so differently by diverse organizations and clinicians. Registries for relatively rare diseases have been useful in the study of other rare malignancies, where existing case definitions masked the presence of multiple entities within the same category. For example, the American Burkitt's lymphoma (BL) Registry (121-123) helped to clarify the fact that a single pathologically defined entity actually consisted of at least two biologically distinct diseases, one characterized by the presence of the Epstein-Barr virus within the tumor cells and different responses to chemotherapy. The Epstein Barr virus (EBV) – associated BL has a consistent chromosome translocation (124), is predominant in sub-Saharan Africa and other areas of holoendemic malaria and appears to respond to less aggressive chemotherapy than the non-EBV-associated BL, which is the predominant form in the United States (123).

To improve the evaluation of American Burkitt's Lymphoma, we divided our cases into subgroups based on the quality of the diagnostic pathology material. A similar approach is being taken with the IBCR, which divides patients with IBC into subgroups according to the degree of clinical and pathologic criteria (Table I).

In the first report from the IBCR (62), among the intriguing findings are the large number of patients who have clinical findings involving less than half of the breast, not the AJCC definition of IBC. In fact, most of the patients in our IBC Registry diagnosed by practicing physicians do not present with this classical form. In a significant number of our Caucasian patients, the first symptom was the appearance of a small pink spot, with no obvious peau d'orange or noticeable breast swelling at the beginning. This early manifestation may not be noticed in African-American women, leading to a later diagnosis.

Unfortunately, the diagnosis of IBC is delayed considerably in a large percentage of women because the clinician does not consider IBC, probably because of inexperience with the disease. This problem is not restricted to primary care physicians as we have had patients referred to surgeons with the possible diagnosis of IBC and the patient has been placed on weeks to months of antibiotics. Approximately one third of our patients were given antibiotics for an infection, for up to five months for some before the diagnosis of IBC was made. Young women with a painful breast, a common presenting feature in IBC, were often told that they could not have breast cancer because they were too young and breast cancer is not painful. In our series, however 34% of our IBC patients presented with breast pain. Furthermore, mammography is often not helpful; in our IBCR series to date only 30% of the diagnostic mammograms showed a discrete mass. Our data are

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similar to those of Kushwaha et al (125) who reported that a mass could be detected in only 15% of their cases. In contrast is the report by Dershaw et al. (126) who observed discrete masses in 21/22 of their IBC patients. In general, however, not only the diffuseness of the tumor but its frequent occurrence in young women with dense breasts interferes with the diagnosis.

Studies are now in progress to test the tissues from the patients in this Registry by a number of molecular techniques to determine if there are different identifiable subgroups of IBC.

5.2   Molecular Biology

A number of molecular approaches are currently being pursued to understand more thoroughly the etiology, pathogenesis and control of aggressive breast cancer and IBC. There are numerous examples of molecular markers being important tools to identify sub-groups of disease which could have important etiologic and prognostic implications. Non-Hodgkins lymphoma (NHL) provides many such examples, with B and T-cell markers now being used extensively in classification . In one form of NHL the identification of human T-lymphotropic virus type-I (127) is used to distinguish classic adult T-cell lymphoma from morphologically similar tumors, a critical factor in understanding the etiology of this tumor. In another form of NHL, Burkitt's lymphoma, at least two subtypes have been defined with the detection of Epstein-Barr virus in the tumor cells of some patients being associated with specific chromosome translocations and other genetic markers (124). It is hoped that similar molecular efforts can be utilized to better define aggressive breast in general and IBC in particular.

As noted in the Introduction, "locally advanced breast cancer" is a completely inappropriate term to be used for IBC because it is apparent that the disease is systemic when first detected. In addition to the invasion of the dermal lymphatics, microemboli are another hallmark of IBC and the spread of the these tumor cells systemically explains why successful treatment of IBC relies primarily on neoadjuvant therapy which is more likely to destroy tumor cells before they have had an opportunity to establish their defenses. It is likely that the increased invasiveness of IBC as compared to non-IBC breast cancer has some molecular counterparts. Several that have been suggested include increased angiogenesis (41), the loss of expression of a novel gene called LIBC (128) and the increased expression of e-cadherin (129). Reasonable mechanisms have been proposed for each of these observations. Angiogenesis as identified by increased microvessel density (MVD) was identified in Tunisian breast cancer patients with objective signs of IBC as compared to other Tunisian breast cancer patients without these signs. Increased angiogenesis is associated with rapid tumor growth as the increased vasculature helps to nourish the tumor. (130). Loss of LIBC was found in a study by van Golen et al. (128) where they investigated 29 IBC and 19 non-IBC stage III archival breast samples and they found a significant difference in the expression of theLIBC gene which was expressed in only 20% of the IBC tumors and in 79% of the non-IBC tumors. They also found that transcript T6, RhoC GTPase was overexpressed in 90% of the IBC

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samples, in comparison with only 38% of the non-IBC samples. When comparing the concordance of having both of these genes altered, they found that the loss of LIBC and the overexpression of RhoC occurred in 91% of the IBC tumors whereas concordance was not seen in any of the non-IBC samples. In Kleer et. al.'s study of 20 IBC and 22 non-IBC matched by stage, they found a strong association between E-cadherin and IBC. All the IBC patients' tumors expressed E-cadherin, whereas only 68% of the non-IBC patients' tumors expressed the protein, and the intralymphatic tumor emboli in the IBC cases also expressed E-cadherin (129). Using a human/mouse model of IBC (where human breast carcinoma was grafted in scid/nude mice), Alpaugh et al. (131) found a 10-20 fold overexpression of E-cadherin in the IBC xenografts as compared to the non-IBC xenographs, and in a later study (132) they found that E-cadherin was involved in the passive dissemination of tumor emboli in IBC.

Among the recent genetic studies, Lerebours et al. (133) reported more genetic alterations in IBC patients compared to non-IBC patients. Specifically they found loss of heterozygosity (LOH) patterns in IBC patients that that were less frequent in non-IBC patients and that LOH patterns differed between patients with localized and extensive breast inflammation. They also found that extensive breast inflammation at the first clinical examination was associated with a poorer outcome and the overall frequency of LOH was also higher in this group. While the progress being made in the laboratory is highly encouraging, much remains to be done.

Another interesting tool that is being applied to IBC is the investigation of viral footprints. Viral studies in breast cancer have a long history (for a review, see Robert-Guroff M, Buehring GC (134) with early virologic techniques (including electron microscopy) having their basis in the study of the mouse mammary tumor virus (MMTV) as a model for a human breast cancer virus. A focus on the relationship of MMTV-associated antigens and molecular sequences to aggressive breast cancer began in 1984 when we applied the findings of Sol Spiegelman and his colleagues to our studies of aggressive breast cancer in Tunisia. Spiegelman's laboratory had noted that human breast cancers contained an antigen that cross-reacted with the gp-52 of MMTV (135, 136) and in our initial applications to the Tunisian study, a far higher proportion of cases (70%) were noted to have this antigen than had been found in U.S. cases (30%) (76). These findings are finding support in preliminary studies using more recent molecular techniques (137, 138) with a tendency for more MMTV-related antigenic and molecular expression in the more aggressive PEV cases than the non-PEV controls (139) . At the present time, studies are in progress to investigate further the geographic patterns of these MMTV-like sequences and there is no definite relationship to aggressiveness, but in view of the apparent increase in aggressiveness when a breast cancer arises during pregnancy, the increased incidence of MMTV-related sequences in breast cancer associated with pregnancy and lactation (62% vs. 30-38% in U.S. cases) (140) is intriguing. Whether or not these sequences prove to be truly related to a human breast cancer virus or to aggressive breast cancer, the definition of subgroups of breast cancer by current laboratory methods is a promising field since such approaches have been useful in classifying other malignancies, such as Burkitt's lymphoma and other non-Hodgkin's lymphoma.

5.3   Epidemiologic Studies

5.3.1   International Patterns

International comparisons regarding the incidence of aggressive breast cancer and IBC are extremely difficult because of differences in case definition and the quality of the data in different registries. Based on the data available, however, current research into the patterns in different countries is extremely important. Several studies, for example, indicate that Africa has a higher proportion of cases of aggressive breast cancer compared to the United States (72, 141-145). The studies in Sub-Saharan Africa are not as population-based as in north Africa and one of the major concerns in case definition, as in all countries, is distinguishing IBC from neglected or locally advanced breast cancer. As the methods for defining aggressive breast cancer on a pathologic and molecular basis evolve, however, international comparisons should be come more feasible.

The early reports indicating that north Africa had a significantly higher proportion of patients with aggressive breast cancer (PEV) and particularly those with clinical signs of IBC (PEV-2 and PEV-3) than virtually any other country is an observation that is now being confirmed and extended by standardized methods. The earlier study at the ISA in Tunisia went beyond the well documented clinical findings and showed that the aggressive breast cancer patients had notable differences in pathologic features (146) hormonal patterns (147), and molecular patterns (primarily micro-vessel density (41) than the non-aggressive cases, confirming the validity of the PEV-2 and PEV-3 classification at that time. Another intriguing finding was the identification of an antigen indistinguishable from the gp-52 of the mouse mammary tumor virus in 70% of Tunisian breast cancer cases vs approximately 30% of U.S. cases (76), somewhat more apparent in the PEV cases than the non-PEV cases (139), but also demonstrating an overall increase in all Tunisian cases. These findings are currently being confirmed by comparable studies using current molecular techniques (148).   A more recent report from Tunisia by another group of ISA investigators provided an interesting follow-up through a national survey of breast cancer patients (141). This study included breast cancer patients throughout Tunisia between Jan. 1, 1994 through Dec. 31, 1994 and compared their findings with the report by Tabbane et al. focused on patients at the Institut Salah Azaiz, the major cancer center, between 1969-1974. The current study found the mean clinical tumor size to decrease 5-6 mm every 10 years from 63.9 mm in 169-974, 55.8 mm 1981-5, and 49.5 mm in 1994. Concomitantly, the percentage of patients with any objective clinical finds of IBC (including PEV 2, which involves less than half of the breast) represented only 23.2% of the 1994 cases vs. 55.2% in the earlier ISA series. The percentage of PEV 3 or T4d cases, comparable to IBC In the AJCC classification, declined from 48.7% in the early series to 6.2% in the 1994 series. These data suggest that the proportion of cases with aggressive breast cancer is decreasing, providing strong support for the importance of environmental factors on the etiology of aggressive breast cancer. The difficulty in dissecting neglected or locally advanced breast cancer from aggressive breast cancer is described in a Nigerian study (143) , where a series of

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116 Nigerian women seen at the University of Benin Teaching Hospital from 1974-79. Slightly over 10% (12 patients) of the Nigerian patients were either pregnant or lactating and 99 (85.3%) of the study group presented with TNM Stages III and IV disease. Evidence for tumor aggressiveness is provided by the pathologic observation that 50% of the patients had anaplastic carcinomas.

5.3.2   U.S. patterns

As the SEER Registry improves its identification of IBC and we learn how to better use the existing data, it is possible to re-examine the earlier reports (60, 61) on IBC patterns in the United States. We are again analyzing and updating the trends in the incidence of IBC and survival with this disease using new as well as old SEER classifications. We have analyzed the incidence of IBC and survival with this disease using new as well as old SEER classifications. The SEER Registry has had several modifications of its identification of IBC as a clinical entity, the latest being a new code (998) established in 2002 which is included under Extent of Disease. This code is used for diffuse tumor involving more than ¾ of the breast or inflammatory breast cancer. In our current re-evaluation of the SEER data (149) using comparable methods to the original report (60) to identify clinically as well as pathologically identified IBC, we found that between the three-year intervals of 1975-1977 and 1998-2000, the incidence of IBC in both African-American and Caucasian women has more than doubled with the incidence in African-American women being 50% higher (1.7/100,000 vs. 1.1/100,000 in Caucasians). Survival from this disease in African-American women was also significantly shorter than for Caucasian women, approximately 51 months vs. 113 months (149).

5.3.3   Risk Factors

As noted above, there is evidence that the risk factors for developing IBC and other aggressive breast cancers differ significantly than the risk factors for breast cancer in general. Studies have shown that reproductive factors known to decrease the risk of breast cancer have an adverse effect on prognosis. Mourali et al. (75) found that late age at menarche, an established risk factor for decreased risk of developing breast cancer, was associated with a increased risk of developing PEV, and they observed that for the patients for whom they had information on date of first pregnancy, 14 of the 15 patients who had their first births at the age of 18 or younger were diagnosed as PEV positive. And in Korzeniowski et al.'s study they found that reproductive factors known to decrease risk, specifically late menarche and parity, were associated with an adverse impact on survival (55).

Based on the results of a pilot study done by Veneroso et al in 1997 (150) we are presently conducting a study on risk factors for aggressive breast cancer. The pilot study was a case-case study of 215 breast cancer patients seen at the George Washington University Medical Faculty Associates. 215 patients were eligible for the study. Tumor aggressiveness was defined by tumor grade and breast cancer patients with tumors that were not aggressive were compared to breast cancer patients with aggressive tumors. The data showed women who had their first child before the age of 20 had about a 3 times greater odds of having an aggressive cancer, ever users of OC had lower odds of

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aggressive cancer than never users, but the longer they used OC, the worse their odds for an aggressive cancer, and women who were diagnosed at an early age had a 4% greater odds for each year younger at diagnosis. The identification of risk factors for aggressive breast cancer in general and IBC in particular is likely to be enhanced by the identification of better and more specific case definitions.

5.4   Treatment

A number of treatment trials are being carried out at large institutions such as the National Cancer Institute in Bethesda and MD Anderson Hospital in Texas which involve various approaches such as inhibition of angiogenesis, vaccines, bone marrow transplants and new agents or combination of agents. Some of these new approaches as well as the current standard approach to the management of IBC have been summarized recently by Cristofanilli et al. (58).

6.   SUMMARY

Aggressive breast cancer is a well recognized but poorly understood phenomenon that has a particularly important impact on women of African descent. The poor survival of African-American women compared to any other U.S. racial/ethnic group is well documented, and this chapter describes the evidence that this adverse outcome is not solely related to barriers to care. The current weight of epidemiologic evidence indicates that tumor aggressiveness results primarily from environmental rather than genetic factors, leading to the possibility that more detailed studies will provide opportunities to reduce the risk of developing an aggressive breast malignancy. The growing success in molecular epidemiology, which is enhancing the opportunity to compare a wide variety of patients in countries throughout the world, should greatly improve our ability to understand the etiology and the possibility of control of aggressive breast cancer.

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